REMARKS

Status of the Application:

This paper is filed in response to the Office Action mailed October 4, 2006 (hereinafter, the "Office Action"). At the time the Office Action was mailed, claims 1-53 were pending in the application. Claims 2-6 and 9-53 have been conditionally withdrawn without prejudice, subject to the restriction requirement in the Office Action dated June 30, 2006. In this response, claims 1 and 8 have been amended. Original claim 7 has been included in the listing of pending claims, for reasons discussed *infra*. Therefore, upon entry of the instant amendment, claims 1, 7, and 8 will remain before the Examiner for reconsideration.

Response to Restriction Requirement:

As acknowledged in the Office Action (page 2, paragraph 1), in the response filed on July 14, 2006, Applicants elected the Group I invention, identified in the Office Action dated June 30, 2006, as claims 1, 7, and 8, which are directed to polypeptides encompassing SEQ ID NOS:1-5 and 115-119. There was also a species election of SEQ ID NO: 115 as required by the Examiner. In the instant Office Action, it is stated that claim 7 (directed to peptides having SEQ ID NOs: 1-5) is withdrawn as a non-elected invention. Applicants disagree; while SEQ ID NO. 115 was elected, as described herein in detail, the scope of claim 1 is broad enough to cover the dependent claims, specifically claims 7 and 8. In light of the amendment to claim 1, however, Applicants respectfully traverse the rejections under 35 USC § 112 and the rejection under 35 USC §102(e) is also traversed. In the instant response, original claim 7 has been included in the pending claim set. The inclusion of claim 7 is believed to be consistent with the previous election of the Group I claims and SEQ ID NO:115, and it is submitted that claim 7 is properly dependent from claim 1, as amended herein. Accordingly, Applicants respectfully request consideration of claims 1, 7 and 8 in the instant application.

The inventive concept should not be, and is not limited to, a single PEGulated species of a single amino acid sequence. This would unduly restrict the scope of the invention and does not

provide meaningful protection over the full scope of the invention. The novel peptides of SEQ ID NOS: 1-5 and 115-119 possess as common features mutations at specific amino acid residues, the percent homology called for in the claims (with SEQ ID NO: 1 having 100% homology except for a terminal cysteine), and the ability to act as VPAC2 receptor agonists. The mutations are designed to improve stability and prolong half-life of the peptides, which were problems associated with prior art non-mutated forms of related peptides with VPAC2 receptor agonist function, as described, e.g., in WO 01/23420 (see, e.g., instant specification, page 41, paragraph 177).

The family of peptides of the instant invention was designed to include, e.g., mutations of the asparagine residues to glutamine residues at positions 9 and 28 of the endogenous peptide, PACAP-27 to improve stability and prolong half-life. (See, e.g., specification at page 41, paragraph 177, describing specific mutations.) In addition SEQ ID NOS:115-119 are polypeptides of the invention that are PEGylated at the C-terminal cysteine via a maleimide linkage.

For convenience, a comparison of the amino acid sequence of the peptides that are included in the claims (i.e., SEQ ID NOS:1-5 and 115-119) is shown in Table A, attached hereto as Exhibit A. As can be seen in Table A, SEQ ID NOS:1-5 and 115-119 of the elected invention comprise a genus of very similar peptide sequences having greater than 90% sequence homology among the species, differing from one another generally by either one or two amino acids (amino acids showing differences from those of SEQ ID NO:115 are shaded in Table A). For simplicity, derivative moieties such as acetyl or PEG groups are not shown in Table A; however, see sequence listing or Fig. 1 of the application for details regarding derivative structures.)

The higher-numbered amino acid sequences (SEQ ID NOS: 115-119) are identical to the corresponding lower-numbered sequences (SEQ ID NOS: 1-5) sequences except for the addition of a cysteine at the C-terminus. The cysteine is used to derivatize the peptides with a polyethylene glycol (PEG) moiety.

In the reply filed July 14, 2006, Applicants elected SEQ ID NO:115 (PEGylated form of SEQ ID NO:1) for further prosecution, in response to the restriction requirement. By comparing the sequences shown in Table A, it is apparent that the amino acid sequences of SEQ ID NOS:1-5 and SEQ ID NOS: 116-119 are fragments, derivatives or variants (as the terms are defined in the specification) of SEQ ID NO:115 that share at least 90% sequence homology with the amino acid sequence of SEQ ID NO:115 and have the VPACP2 receptor agonist activity. Given the close relationship among all of the mutated sequences of the Markush group comprising SEQ ID NOS:1-5 and 115-119, it is respectfully requested that upon a finding of patentability of claims directed to SEQ ID NO:115, claims directed to other members of the Markush group, i.e., SEQ ID NOS:1-5 and 116-119 be rejoined.

Rejections Under 35 U.S.C. § 112:

Claims 1 and 8 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite due to alleged ambiguity caused by reference of the claims to non-elected subject matter. As amended herein, claim 1 recites the elected sequence, SEQ ID NO:115, and claims 7 and 8 recite specific SEQ ID NOS: 1-5 and 116-119, respectively, that are consistent with the election of SEQ ID NO:115, as discussed above. Accordingly, it is submitted that this rejection has been overcome and its withdrawal is respectfully requested.

Claim 1 was rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of written description due to the recitation of the term "variants, derivatives, and fragments" of SEQ ID NO:115, without structural and functional limitations. Applicants respectfully disagree; these terms were never unlimited in scope because they are defined in the specification. (See, paragraphs 47, 50, and 52-58). In the interest of furthering prosecution, however, claim 1 was amended so that it recites only fragments, derivatives or variants of SEQ ID NO:115 having both the functional requirement that the peptide must possess VPAC2 receptor agonist activity function, and the structural requirement that it must share at least 90% sequence homology to the amino acid sequence of SEQ ID NO:115.

Similarly, the rejection of claim 1 under 35 U.S.C. § 112, first paragraph, for lack of enablement due to the recitation of the term "variants, derivatives, and fragments" of SEQ ID NO:115 without structural and functional limitations is traversed. As discussed above in connection with the written description rejection, claim 1 has been amended to recite the respective functional and structural limitations of VPAC2 receptor agonist activity, and 90% or greater sequence homology to SEQ ID NO:115.

The Office Action (at page 5) states that the amount of direction provided in the specification is limited to a specific species of SEQ ID NO:115, and further states that one skilled in the art would require empirical experimentation in order to determine the changes to SEQ ID NO:115 sequence that would preserve functionality. Applicants respectfully disagree.

As discussed above, claim 1 does not recite unlimited variants, derivatives, and fragments of SEQ ID NO:115. Furthermore, the specification provides abundant teaching and working examples regarding not only SEQ ID NO:115, but numerous 29-32 amino acid variants of SEQ ID NO:115. (See, e.g., Fig. 1, listing specific sequences of 152 similar peptides of the invention; the description of functionally equivalent polypeptides (paragraph 047); and the teaching of how to test for functional polypeptides in a quantitative manner in an assay, e.g ., as described in Example 7.) Applicants respectfully disagree with the statement that the number of variants, derivatives, and fragments is unlimited.

The Office Action further states on page 6 that no working example is provided to determine whether a change in the domains of SEQ ID NO:115 is functional, and concludes that one of skill in the art could not practice the invention without undue experimentation. Claim 1, as amended, requires a specific functional activity. Applicants respectfully direct the attention of the Examiner to the studies described in worked Example 7, involving assays of VPAC2 and VPAC1 receptor agonist activity using six different variants of the peptides of the invention (results shown in Table 1, page 45). Referring to Table 1, peptides of the invention identified in the table as P5, P7, P8, and P12 + PEG correspond, respectively, to SEQ ID NOS:1, 5, 2, and 115. The results show that

peptides identified as P5, P7, P8, P12 and P12 + PEG are all potent agonists of the VPAC2 receptor, activating the receptor to 100% of the maximal level of receptor activation achieved by an endogenous control peptide, PACAP-27. Furthermore, advantageously, the identified peptides are selective VPAC2 receptor agonists, possessing very weak agonist activity on VPAC1. In contrast, the control peptide PACAP-27 is a potent agonist of both VPAC1 and VPAC2 receptors. (See, e.g., specification at paragraph 189.) Additionally, the superior stability of pharmaceutical compositions comprising peptides of the invention having sequences represented by SEQ ID NOS:1, 5, and 6, relative to a composition comprising a control peptide, is described in worked Examples 8 and 9, with results shown in Figs. 6 and 7.

In conclusion, for the above-stated reasons, Applicants respectfully submit that the instant specification provides abundant teaching, including worked examples, to enable one of skill in the art to practice the invention over the full scope of the claims without undue experimentation, and accordingly request reconsideration and withdrawal of the rejection of claim 1 for lack of enablement.

Rejection Under 35 U.S.C. § 102:

Claim 1 was rejected under 35 U.S.C. § 102(e) as being anticipated by Pan et al. (US 6,972,319; "Pan"). According to the Office Action, Pan discloses many peptides that are 89% identical in amino acid sequence to the claimed SEQ ID NO:115, and meets the limitation of the term claimed because no structure is claimed, and Pan encompasses the term "variants, derivatives and fragments."

As discussed above, claim 1, as amended, does not recite unlimited variants, derivatives and fragments, but rather recites only SEQ ID NO:115 and fragments, derivatives and variants thereof having homology of at least 90% to the amino acid sequence of SEQ ID NO:115 and VPAC2 receptor agonist activity. Therefore, claim 1 as amended is not anticipated by the sequences disclosed in Pan.

Furthermore, the sequences encompassed by claim 1 as amended herein (and claims 7 and 8) cannot be held obvious in view of Pan. At the time of filing of the instant application, both the instant application and the application that issued as the Pan patent were commonly owned by Bayer Pharmaceuticals Corporation. Accordingly, the Pan patent is disqualified as prior art under 35 U.S.C. §103(c)(1).

Applicants also consider that many, if not all, of the restricted claims should be rejoined. In particular, claims 2-6, and 10-53 should be rejoined as all relate to claim 1.

Conclusion:

Applicants consider that all claims are allowable as written and respectfully request early and favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicants' attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney.

Respectfully submitted,

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AA	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
SEQ ID NO:																																
1	H	S	D	A	V	F	T	D	Q	Y	T	R	L	R	K	Q	V	A	A	K	K	Y	L	Q	S	I	K	Q	K	R	Y	
2	H	[illegible]	D	A	V	F	T	D	Q	Y	T	R	L	R	K	Q	V	A	A	K	K	Y	L	Q	S	I	K	Q	K	R	Y	
3	H	S	D	A	V	F	T	D	Q	Y	T	R	L	R	K	Q	M	A	A	K	K	Y	L	Q	S	I	K	Q	K	R	Y	
4	H	S	D	A	V	F	T	D	Q	Y	T	R	L	R	K	Q	V	A	A	K	K	Y	L	Q	S	I	K	Q	K			
5	H	[illegible]	E	A	V	F	T	D	Q	Y	T	R	L	R	K	Q	V	A	A	K	K	Y	L	Q	S	I	K	Q	K	R	Y	
115	H	S	D	A	V	F	T	D	Q	Y	T	R	L	R	K	Q	V	A	A	K	K	Y	L	Q	S	I	K	Q	K	R	Y	C
116	H	[illegible]	D	A	V	F	T	D	Q	Y	T	R	L	R	K	Q	V	A	A	K	K	Y	L	Q	S	I	K	Q	K	R	Y	C
117	H	S	D	A	V	F	T	D	Q	Y	T	R	L	R	K	Q	M	A	A	K	K	Y	L	Q	S	I	K	Q	K	R	Y	C
118	H	S	D	A	V	F	T	D	Q	Y	T	R	L	R	K	Q	V	A	A	K	K	Y	L	Q	S	I	K	Q	K	C		
119	H	[illegible]	E	A	V	F	T	D	Q	Y	T	R	L	R	K	Q	V	A	A	K	K	Y	L	Q	S	I	K	Q	K	R	Y	C

EXHIBIT A

Table A, showing a sequence comparison of SEQ ID NOS:1-5 and 115-119. SEQ ID NOS: 115-119 further comprise a PEG moiety (not shown) attached to the terminal cysteine (C) on the C-terminus of the peptide.